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Letter to the Editor
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Acute Pericarditis with High Anti-Nuclear Antibody Titers Following BNT162b2 mRNA COVID-19 Vaccination

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INTRODUCTION

Messenger RNA (mRNA) vaccines, including mRNA-1273 (Moderna) and BNT162b2 (Pfizer/BioNTech) have been approved for severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) since late 2020. Acute perimyocarditis following these mRNA vaccinations has been reported.[1,2]

The underlying mechanisms of coronavirus disease 2019 (COVID-19) vaccine-related pericarditis are unclear, and thus supportive care, non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, and steroids remain the mainstream treatments. Current guidelines for acute pericarditis stress that corticosteroids should be used with caution, and suggest that their use be limited to second-line therapy or when there is an underlying autoimmune disease.[3] New-onset or flares of autoimmune diseases after COVID-19 infection and COVID-19 vaccinations have increasingly been reported.[4,5] Herein, we report, to the best of our knowledge, the first case in Taiwan of a patient with acute pericarditis and high antinuclear antibody titers following BNT162b2 vaccination.

CASE

A 23-year-old female without systemic diseases came to our outpatient clinic for acute chest pain 10 days after her first dose of BNT162b2 (Pfizer/BioNTech) vaccination. She described her chest pain as a stabbing sensation, which was aggravated by lying down and relieved by sitting up and leaning forward. There was no shortness of breath, cold sweating, or limb edema. Faint friction rub was heard during a careful physical examination. Initial electrocardiography (ECG) did not show significant PR or ST-segment abnormalities (Figure 1A). Laboratory tests showed normal cardiac enzymes (CPK: 45 U/L, CKMB: < 10 U/L, troponin I: 3 ng/L). Echocardiography showed good left ventricular ejection fraction of 67% without regional wall abnormalities or pericardial effusion (Figure 2A). Her condition did not improve after initial treatment with supportive care and colchicine for 1 week. Under the impression of acute pericarditis, she was admitted to our ward.

After admission, we gave her acemetacin 60 mg and kept colchicine 0.5 mg daily. Follow-up laboratory tests showed no obvious elevation of cardiac enzymes, and virology studies were negative. However, a high positive antinuclear antibody (ANA) titer (1:640) with a nuclear dense fine speckled (AC-2) pattern was noted. Specific antibodies, including anti-double stranded DNA (anti-dsDNA) antibodies were all negative (Table 1). Her chest pain had not improved at all on hospital day 3. ECG on that day showed mild PR depression in lead II and III (Figure 1B), which might suggest localized pericardial inflammation. Methylprednisolone 40 mg daily was prescribed, and her chest pain then subsided on the next day. On hospital day 5, cardiac magnetic resonance (CMR) imaging showed normal wall motion, no abnormal late gadolinium enhancement (LGE) in the myocardium, and normal pericardium without enhancement or peripheral effusion (Figure 2C, 2D). Oral prednisolone was switched when she was discharged on hospital day 8. One week after discharge, follow-up ECG showed PR depression in

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lead II and III had completely resolved (Figure 1C). Echocardiography demonstrated a small amount of pericardial effusion (Figure 2B). The ANA titer was stable at the level of 1:1280 in the first two months after discharge. Since her chest pain resolved, we tapered prednisolone smoothly. She is currently receiving low-dose prednisolone and is being followed up monthly at our outpatient department.

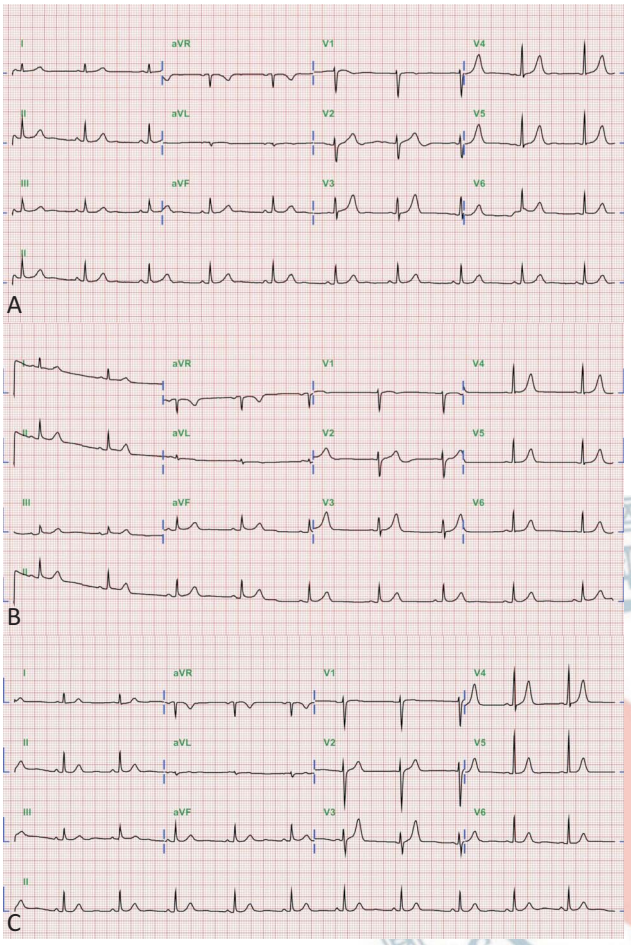

Figure 1. *Serial electrocardiography (ECG) at outpatient clinics and hospital day 3. (A) The initial ECG did not show significant PR or ST-segment abnormalities. (B) The ECG on hospital day 3 showed PR depression in lead II and III. (C) The PR depression in lead II and III had resolved in the ECG one week after discharge.*

DISCUSSION

Myocarditis or pericarditis is inflammation of the myocardium or pericardium, respectively, and it can be caused by various factors. Viral myocarditis is the most

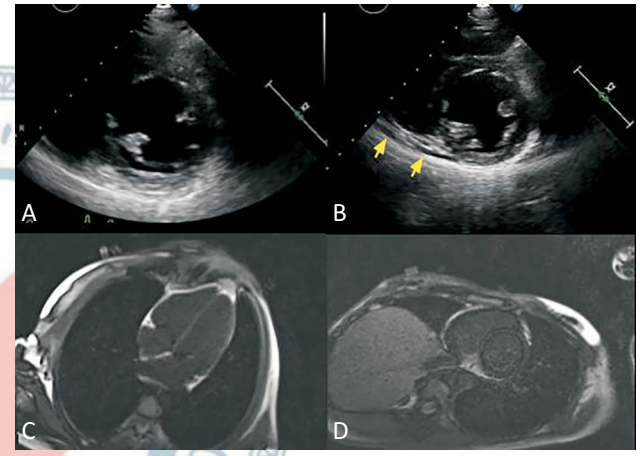

Figure 2. *Cardiac images of echocardiography and myocardial magnetic resonance imaging with late gadolinium enhancement. (A) At admission, echocardiography under short axis showed no pericardial effusion. (B) One week after discharge, echocardiography showed a minimal amount of pericardial effusion (arrow). (C, D) Delayed enhanced phase-sensitive inversion-recovery (PSIR) image showed no abnormal delayed enhancement over the myocardium and pericardium.*

Table 1. Serology studies for autoimmune disease on hospital day 1

	Reference	Unit	Value
ANA	-	-	Positive (1:640)
ANA pattern	-	-	Nuclear dense fine speckled
Anti-dsDNA	< 10	IU/mL	1.1, Negative
Anti-cardiolipin IgG	0-10	U/mL	1.7, Negative
Anti-β2-GP1 IgG	0-7	EU/mL	< 0.6, Negative
Anti-Sm antibody	< 100	AU/mL	25, Negative
Anti-RNP	< 100	AU/mL	18, Negative
Anti-Ro antibody	< 100	AU/mL	13, Negative
Anti-La antibody	< 100	AU/mL	13, Negative
C3	87-200	mg/dL	118.9
C4	19-52	mg/dL	22.3

ANA, antinuclear antibody; Anti-dsDNA, anti-double stranded DNA; Anti-RNP, anti-ribonucleoprotein; Anti-Sm antibody, anti-Smith antibody; Anti-β2-GP1, anti-beta2-glycoprotein 1; IgG, immunoglobulin G.

common cause, and it has been reported in SARS-CoV2 patients. With the increasing use of mRNA COVID-19 vaccinations worldwide, the association between acute peri-myocarditis and mRNA COVID-19 vaccination has been increasingly reported.[1,2]

CMR is a sensitive non-invasive imaging tool with 72.7% sensitivity to detect pericardial edema and LGE,[6] and it is also suggested to diagnose pericarditis by the Centers for Disease Control and Prevention (CDC) working case definition.[7] However, the clinical presentation and physical examinations are essential when making a diagnosis. In our case, the clinical diagnosis of pericarditis was supported by typical pericardial chest pain and friction rub in the initial presentation, and the emerging pericardial effusion after discharge also favored the diagnosis. A possible explanation for the lack of LGE in the pericardium and pericardial effusion on CMR may be due to the early disease stage or because she was treated with colchicine, NSAIDs and steroids for days.

Various mechanisms for COVID-19 mRNA vaccine-related pericarditis have been proposed. One hypothesis is that the immune-modified mRNA does not turn down the innate immune response and leads to systemic inflammation.[8] Another hypothesis is molecular mimicry between SARS-CoV-2 spike glycoproteins and self-antigens, including myosin, leading to peri-myocarditis.[9] However, there is currently no evidence supporting vaccination-induced de novo autoimmune disease. Instead, it may trigger an aberrant innate and acquired immune response under certain predisposing conditions.[7,8]

ANAs have been reported to be positive (> 1:40) in 43.4% of cases of idiopathic recurrent pericarditis. A low ANA titer (< 1:160) is often non-specific and asymptomatic, however higher titers may indicate an autoimmune disease, such as systemic lupus erythematosus and sicca syndrome.[4,5] One study reported that ANAs were positive in 17% of cases 6 days after BNT162b2 and mRNA-1273 vaccinations, but that there were no significant changes before and after vaccination.[10] Besides, ANA titers did not increase in most published cases of COVID-19 mRNA vaccine-related pericarditis.

In our case, the patient was a previously healthy young female who suffered from acute pericarditis with high ANA titers (1:640) following COVID-19 mRNA vaccination. While her chest pain was refractory to NSAIDs and colchicine, she responded well to steroids. The clinical course implied that she probably had an aberrant immune response triggered by the COVID-19 vaccination which resulted in autoimmune pericarditis. Although a causal relationship could not be proven in our case, we believe it was not merely a coincidence considering the temporal relationship and lack of other potential triggers.

In conclusion, as shown in our case, a high ANA titer could probably be served as a good indicator for the use of steroids in patients with acute pericarditis following COVID-19 mRNA vaccination, and that it may also be a predictor of response to corticosteroid therapy. To ensure timely steroid therapy, early measurement of ANA in patients with acute pericarditis following COVID-19 mRNA vaccine should be considered.

LEARNING POINTS

Post-vaccination peri-myocarditis following mRNA COVID-19 vaccination is a rare but potentially fatal complication. As shown in our case, a high ANA titer may suggest that steroid could be used earlier in patients with acute pericarditis following COVID-19 mRNA vaccination. Further studies have to verify this speculation.

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DECLARATION OF CONFLICT OF INTEREST

All authors declare no conflicts of interest.

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